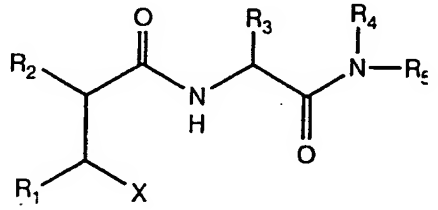
5% CO_2, then centrifuged at 1000 x g for 5 minutes. A specific ELISA for TNF α obtained from R&D Systems Europe Ltd, Abingdon, England is used to measure TNF α levels in the culture supernatants

The average concentration of test compound which inhibits the release of TNF α by 50% relative to the control culture was assessed. The compound of example 5 above had IC_{50} value less than 3.5 μM. μM.

Claims

1. A compound of general formula (I):



(I)

wherein;

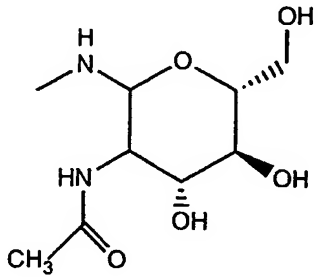
X is -CONHOH or $-CO_2H$;

R_1 is hydrogen, a C_1-C_6 alkyl, C_2-C_6 alkenyl, phenyl, substituted phenyl, phenyl(C_1-C_6 alkyl), heterocyclyl, substituted heterocyclyl, heterocyclyl(C_1-C_6 alkyl), substituted heterocyclyl(C_1-C_6 alkyl), or a group BSO_nA- wherein n is 0, 1 or 2 and B is hydrogen or a (C_1-C_6) alkyl, phenyl, substituted phenyl, heterocyclyl, C_1-C_6 acyl, phenacyl or substituted phenacyl group, and A represents C_1-C_6 alkyl; amino; protected amino; acylamino; OH; SH; C_1-C_6 alkoxy; C_1-C_6 alkylamino; C_1-C_6 alkylthio; aryl(C_1-C_6 alkyl); amino(C_1-C_6 alkyl); hydroxy(C_1-C_6 alkyl), mercapto(C_1-C_6 alkyl) or carboxy(C_1-C_6 alkyl) wherein the amino-, hydroxy-, mercapto- or carboxyl-group are optionally protected or the carboxyl- group amidated; lower alkyl substituted by maleimido, succinimido, naphthalimido, 2,3-dihydro-1,3-dioxo-1H-benz[d,e]isoquinol-2-yl, carbamoyl, mono(lower alkyl)carbamoyl, di(lower alkyl)carbamoyl, di(lower alkyl)amino, carboxy-lower alkanoylamino, pyrrolidino or morpholino;

R_2 is a (C_1-C_6)alkyl, (C_2-C_6)alkenyl, (C_2-C_6)alkynyl, phenyl(C_1-C_6)alkyl,

heteroaryl(C_1-C_6)alkyl, cycloalkyl (C_1-C_6)alkyl or cycloalkenyl (C_1-C_6) alkyl group anyone of which may be optionally substituted by one or more substituents selected from (C_1-C_{10})alkyl, O(C_1-C_6) alkyl, S(C_1-C_6) alkyl, O(C_1-C_6 alkyl)OC_1-C_6 alkyl, S(C_1-C_6 alkyl)OC_1-C_6 alkyl, O(C_1-C_6 alkyl)SC_1-C_6 alkyl or S(C_1-C_6 alkyl)SC_1-C_6 alkyl;

R_3 is **(a)** a group -(C_1-C_6 alkyl)COR_6, or -(C_1-C_6 alkyl)(C_6H_4)XR_6 where X is a group -OCH_2CO, -CO-, -CH_2CH_2CO- or -NHCH_2CO- and R_6 is a group of formula (II):



(II)

or **(b)** (subject to the proviso below) the side chain of a naturally occurring amino acid, which may be protected if functional groups are present, eg by acylation of amino groups and amidation of carboxyl groups; or a group $CR_8R_9R_{10}$ in which each of R_8, R_9 and R_{10} is independently hydrogen, (C_1-C_6)alkyl, (C_2-C_6)alkenyl, (C_2-C_6)alkynyl, phenyl(C_1-C_6)alkyl, hydroxyl, O(C_1-C_6) alkyl, S(C_1-C_6) alkyl, OPh, OCH_2Ph, SPh, SCH_2Ph, halogen, CN, CO_2H, (C_1-C_4)perfluoroalkyl, CH_2OH, CO_2(C_1-C_6)alkyl, or a group phenyl or heteroaryl which is optionally substituted by one or more substituents independently selected from hydrogen, hydroxyl, halogen, CN, CO_2H, CO_2(C_1-C_6)alkyl, $CONH_2$, CONH(C_1-C_6)alkyl, CONH(C_1-C_6alkyl)$_2$, CHO, CH_2OH, (C_1-C_4)perfluoroalkyl, O(C_1-C_6)alkyl, S(C_1-C_6)alkyl, SO(C_1-C_6)alkyl, SO_2(C_1-

C_6)alkyl, NO_2, NH_2, NH(C_1-C_6)alkyl, N((C_1-C_6)alkyl)$_2$, NHCO(C_1-C_6)alkyl, (C_1-C_6)alkyl, (C_2-C_6)alkenyl, (C_2-C_6)alkynyl, (C_3-C_8)cycloalkyl, (C_4-C_8)cycloalkenyl, phenyl or benzyl; or R_8 and R_9 together with the carbon atom to which they are attached form a 3 to 8 membered cycloalkyl or a 5- to 6-membered heterocyclic ring; or R_8, R_9 and R_{10} together with the carbon atom to which they are attached form a bicyclic ring (for example adamantyl);

R_4 is **(i)** a group -(CH(R_7)CONH)$_m$COR_6, wherein m = 0, 1, or 2, R_6 is as defined above, and R_7 is hydrogen or the side chain of a naturally occurring amino acid, which may be protected if functional groups are present, eg by acylation of amino groups and amidation of carboxyl groups;
or **(ii)** (subject to the proviso below) hydrogen, C_1-C_6 alkyl, (C_1-C_4)perfluoroalkyl or a group D-(C_1-C_6 alkyl) wherein D represents hydroxy, (C_1-C_6)alkoxy, (C_1-C_6)alkylthio, acylamino, optionally substituted phenyl or heteroaryl, NH_2, or a mono- or di-(C_1-C_6 alkyl amine;

R_5 is hydrogen or a (C_1-C_6)alkyl group;

provided that at least one of the groups R_3 and R_4 contains a group R_6 as defined above

or a salt, hydrate or solvate thereof.

2. A compound as claimed in claim 1 wherein R_4 is a group -(CH(R_7)CONH)$_m$COR_6, wherein m = 0, 1, or 2, R_6 is as defined in claim 1, and R_7 is hydrogen.

3. A compound as claimed in claim 1 or claim 2 wherein R_1 is hydrogen,

hydroxyl or allyl.

4. A compound as claimed in any of the preceding claims wherein R_2 is iso-butyl, n-pentyl, n-hexyl, n-septyl, n-octyl, cyclohexylpropyl, cyclohexylbutyl, cyclohexylpentyl, phenylethyl, phenylpropyl, phenylbutyl, phenylpentyl, propyloxymethyl or propylsulphanyl.

5. A compound as claimed in any of the preceding claims wherein R_3 is benzyl or t-butyl.

6. A compound as claimed in any of claims 1-4 wherein R_4 is methyl, ethyl, propyl, butyl, hydroxyethyl, hydroxypropyl, 2,2-dimethyl-3-hydroxypropyl, hydroxybutyl, methoxyethyl, ethoxyethyl, methoxypropyl, 2,2-dimethyl-3-methoxypropyl, 2,2-dimethyl-3-ethoxypropyl, 2-ethylthioethyl, 2-acetoxyethyl, N-acetyl-aminoethyl, 3-(2-pyrrolidone)propyl, optionally substituted phenylethyl, phenylpropyl, phenylbutyl and phenylpentyl.

7. A compound as claimed in any of the preceding claims wherein R_5 is hydrogen.

8. A compound selected from the group consisting of;

[4-(N-Hydroxyamino)-2R-isobutylsuccinyl]-L-phenylalaninyl-glycinyl-N-(2-acetamido-2-deoxy-ß-D-glucopyranosyl)-amide;

[4-(N-Hydroxyamino)-2R-isobutylsuccinyl]-L-phenylalaninyl-glycinyl-glycinyl-N-(2-acetamido-2-deoxy-ß-D-glucopyranosyl)-amide;

[4-(N-Hydroxyamino)-2R-isobutylsuccinyl]-O-[(2-acetamido-2-deoxy-ß-D-glucopyranosyl)carboxamidomethyl]-L-tyrosine-N-methylamide;

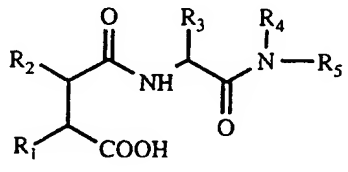
3S-Hydroxy-4-(N-hydroxyamino)-2R-isobutylsuccinyl-L-phenylalaninyl-

glycinyl-N-(2-acetamido-2-deoxy-ß-D-glucopyranosyl)-amide;
and salts, solvates and hydrates thereof.

9. [3S-Allyl-4-(N-hydroxyamino)-2R-isobutylsuccinyl]-N4-(2-acetamido-2-deoxy-α-D-glucopyranosyl)-L-glutamine-N-methylamide and salts, solvates and hydrates thereof.

10. A process for the preparation of a compound as claimed in claim 1 in which X is a hydroxamic acid group (-CONHOH), which process comprises:

(a) coupling an acid of general formula (III)



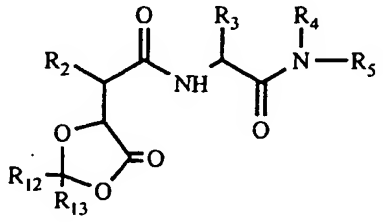
(III)

or an activated derivative thereof with hydroxylamine, O-protected hydroxylamine, or a salt thereof, R_1, R_3, R_4, and R_5 being as defined in general formula (I) except that any substituents in R_1, R_2, R_3, R_4, and R_5 which are potentially reactive with hydroxylamine, O-protected hydroxylamine or their salts may themselves be protected from such reaction, then removing any protecting groups from the resultant hydroxamic acid moiety and from any protected substituents in R_1, R_2, R_3, R_4, and R_5; and

(b) optionally converting a compound of general formula (I) into another compound of general formula (I).

11. A process as claimed in claim 10 wherein an activated derivative of a compound of formula (III) is used and said activated derivative is a pentafluorophenyl, hydroxysuccinyl, or hydroxybenztriazyl ester.

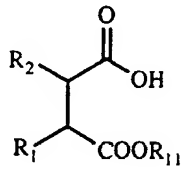
12. A process as claimed in claim 10 or claim 11 wherein (in the special case where R_1 in compound (I) is hydroxy) the hydroxy group R_1 and the adjacent carboxyl group are simultaneously protected as a dioxalone of formula (IV):



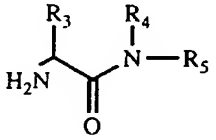
(IV)

wherein the groups R_{12} and R_{13} are derived from a dioxalone forming reagent, and the dioxalone ring being is opened by the reaction with hydroxylamine to give the required hydroxamic acid derivative of formula (I).

13. A process for the preparation of a compound as claimed in claim 1 in which X is a carboxylic acid group (-COOH) which process comprises coupling an acid of formula (V) or an activated derivative thereof with an amine of formula (VI)



(V)



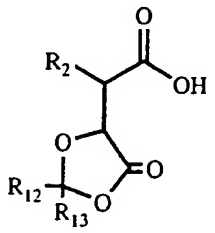
(VI)

wherein R_1, R_2, R_3, R_4, and R_5 are as defined in general formula (I) except that any substituents in R_1, R_2, R_3, R_4, and R_5 which are potentially reactive in the coupling reaction may themselves be protected from such reaction, and R_{11} represents a hydroxy protecting group, and subsequently removing the protecting group R_{11} and any protecting groups from R_1, R_2, R_3, R_4, and R_5.

14. A process as claimed in claim 13 wherein an activated derivative of a

compound of formula (V) is used and said activated derivative is a pentafluorophenyl ester, acid anhydride or acid halides, eg chloride.

15. A process as claimed in claim 13 or claim 14 wherein (in the special case where R_1 in compound (I) is hydroxy) compound (V) has the formula (VII):



(VII)

wherein R_2 is as defined in general formula (I) and the groups R_{12} and R_{13} are derived from a dioxalone forming reagent.

16. A process as claimed in claim 12 or claim 15 wherein the groups R_{12} and R_{13} are hydrogen, alkyl, phenyl or substituted phenyl.

17. A method of management (by which is meant treatment or prophylaxis) of diseases or conditions mediated by MMPs and/or TNF in mammals including humans, which method comprises administering to the mammal an effective amount of a compound as claimed in any one of claims 1 to 9.

18. A compound as claimed in any one of claims 1 to 9 for use in human or veterinary medicine, in the management (by which is meant treatment or prophylaxis) of diseases or conditions mediated by MMPs and/or TNF.

19. The use of a compound as claimed in any one of claims 1 to 9 in the preparation of an agent for the management (by which is meant treatment or prophylaxis) of diseases or conditions mediated by MMPs and/or TNF.

21. A method as claimed in claim 17, a compound for use as claimed in claim 18, or the use as claimed in claim 19, wherein the diseases or condition referred to is one mediated by an MMP.

22. A method as claimed in claim 17, a compound for use as claimed in claim 18, or the use as claimed in claim 19, wherein the diseases or condition referred to is rheumatoid arthritis, osteoarthritis, periodontitis, gingivitis, corneal ulceration or tumour invasion by secondary metastases.

23. A method as claimed in claim 17, a compound for use as claimed in claim 18, or the use as claimed in claim 19, wherein the diseases or condition referred to is one mediated by TNF.

24. A method as claimed in claim 17, a compound for use as claimed in claim 18, or the use as claimed in claim 19, wherein the disease or condition referred to is inflammation, fever, cardiovascular effects, haemorrhage, coagulation and acute phase response, cachexia and anorexia, an acute infection, a shock state, a graft versus host reaction or autoimmune disease.

25. A pharmaceutical or veterinary composition comprising a compound as claimed in any one of claims 1 to 9 together with a pharmaceutically or veterinarily acceptable excipient or carrier.

26. A pharmaceutical or veterinary composition as claimed in claim 25 which is adapted for oral administration.

27. A compound as claimed in claim 1 except that one or more of the hydroxy groups in the group R_6 is protected.

28. A compound as claimed in claim 27 in which the said hydroxy groups are protected as the acetate.

INTERNATIONAL SEARCH REPORT

Inte· ·nal Application No
PCT/GB 94/00808

A. CLASSIFICATION OF SUBJECT MATTER
IPC 5 C07H13/04 C07K9/00 A61K31/70

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 5 C07H C07K A61K C07C

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP,A,0 489 577 (CELLTECH LIMITED) 10 June 1992 cited in the application see the whole document ---	1,8,10, 13, 17-19, 25-27
P,A	WO,A,94 02447 (BRITISH BIO-TECHNOLOGY LIMITED) 3 February 1994 see the whole document -----	1,8,10, 13, 17-19, 25-27

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

2

Date of the actual completion of the international search	Date of mailing of the international search report
21 July 1994	03. 08. 94
Name and mailing address of the ISA European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Authorized officer Moreno, C

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

ternational application No.
PCT/GB94/00808

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 17,21-24
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claims 17 and 21 to 24 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. [ ] As all searchable claims could be searches without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

.nformation on patent family members

Inte: ;nal Application No
PCT/GB 94/00808

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
EP-A-0489577	10-06-92	AU-A-	9017391	25-06-92
		AU-A-	9023391	25-06-92
		EP-A-	0489579	10-06-92
		WO-A-	9209564	11-06-92
		WO-A-	9209565	11-06-92
		GB-A-	2255339	04-11-92
		GB-A-	2255340	04-11-92
		HU-A-	61973	29-03-93
		JP-T-	5503719	17-06-93
		JP-T-	5503720	17-06-93
		US-A-	5300501	05-04-94
WO-A-9402447	03-02-94	AU-B-	4715293	14-02-94
		AU-B-	4715393	14-02-94
		WO-A-	9402446	03-02-94
		GB-A-	2268933	26-01-94
		GB-A-	2268934	26-01-94